Melanoregulin-Anaplastic Lymphoma Kinase (ALK), a Novel ALK Rearrangement That Responds to Crizotinib in Lung Adenocarcinoma

To the Editor:

The rearrangement of anaplastic lymphoma kinase (ALK) is a distinct driver in NSCLC, which is found in 3% to 5% of patients with NSCLC.1 In NSCLC, many fusion partners of ALK have been reported, and the most common ALK rearrangement is echinoderm microtubule–associated protein like 4–ALK.2 ALK rearrangements are correlated with response to ALK tyrosine kinase inhibitors (TKIs). Here, we report a novel melanoregulin (MREG)-ALK fusion, which is sensitive to crizotinib, in a patient with lung adenocarcinoma and brain metastasis.

A 65-year-old nonsmoking Chinese woman was admitted to the local hospital with cough since 2 months. She had no fever, expectoration, or headache. Computed tomography scans of her chest reported an irregular nodular mass in the left main bronchial wall and the left lingual lobe, with a narrowing of the left lower lobe bronchi (Fig. 1A). Meanwhile, cranial computed tomography and magnetic resonance imaging revealed a space-occupying lesion in the frontal lobe, accompanied by bone destruction, which was considered a metastatic tumor (Fig. 1B). A biopsy through fiberoptic bronchoscopy was performed, and pathologic analysis reported a poorly differentiated lung adenocarcinoma with mucin production in cytoplasm (Fig. 1C and D). Formalin-fixed, paraffin-embedded specimens from bronchoscopy biopsy were sent for genomic testing by next-generation sequencing. Results revealed that MREG promoter was fused to ALK exon 20, leading to a novel MREG-ALK fusion gene with a mutant allele frequency of 13.09% (Fig. 2A and B). At the same time, immunohistochemistry was performed with the Ventana D5F3 (Roche), revealing the diffuse expression of ALK in the cytoplasm of tumor cells (Fig. 2C). Break-apart fluorescent in situ hybridization probe (Vysis FISH, Abbott) reported a separation of ALK (Fig. 2D). The patient received an ALK TKI crizotinib orally at a dose of 250 mg (twice daily) after our pathologic diagnosis. The tumor size decreased both in the lung and in the brain with an impressive symptomatic improvement after 3 months of therapy (Fig. 1E and F).

Multiple ALK fusion partners have been reported in NSCLC, and break points vary across patients even with the same partner gene. These make it complicated when treatment and prognosis are concerned because responses to ALK TKIs are heterogeneous for different ALK fusion variants.3,4 To our knowledge, MREG has not been previously reported as a fusion partner of ALK. MREG, the product of the Mreg<sup>dm</sup> located at 2q35, has been shown to act as a factor in organelle biogenesis, maintain melanosome size and distribution, drive melanosome transfer from melanocytes to keratinocytes, regulate membrane fusion, and suppress the invasion and proliferation of thyroid cancer cells.5 In our present case, the break points of this fusion were located in the promoter of MREG and exon 20 of ALK. We speculate that the fusion of the MREG promoter activates the expression of ALK as indicated in other ALK fusion events. Moreover, the patient harboring MREG-ALK fusion reported a response to the ALK inhibitor crizotinib.

To our knowledge, this is the first case to present a patient with lung adenocarcinoma harboring a new fusion of ALK rearrangement (MREG-ALK) showing response to crizotinib. Our finding expands the spectrum of ALK fusion variants that should be added to the list of ALK fusion genes.
Figure 1. Radiologic and pathologic features of lung adenocarcinoma with brain metastasis. (A) CT scan of the thorax revealed an irregular nodular mass in the left main bronchial wall and the left lingual lobe (arrow). (B) Cranial MRI revealed a space-occupying lesion in the frontal lobe, accompanied by bone destruction (arrow). (C) H&E staining showed a poorly differentiated lung adenocarcinoma, original magnification ×200. (D) AB/PAS staining showed adenocarcinoma with mucin production in cytoplasm, original magnification ×400. (E, F) CT scan of thorax (E, arrow) and cranial MRI (F, arrow) showed the size of tumor decreased after 3 month therapy of crizotinib. AB/PAS, alcian blue/periodic acid-Schiff; CT, computed tomography, HE, hematoxylin and eosin; MRI, magnetic resonance imaging.

Figure 2. Identification of a novel MREG-ALK fusion by next-generation sequencing. (A) Sequencing reads of ALK and MREG were reported by the Integrative Genomics Viewer. (B) Schematic structure of the genomic DNA sequence revealed fusion points for the MREG-ALK fusion gene. (C) Ventana ALK (D5F3) IHC assay revealed diffuse expression of ALK in the cytoplasm of tumor cells; original magnification, ×400. (D) Break-apart FISH probe in the tumor sample revealed split red-green or single red dots, indicating ALK fusion. ALK, anaplastic lymphoma kinase; FISH, fluorescent in situ hybridization; IHC, immunohistochemistry; MREG, melanoregulin.
Identification of a Novel Osimertinib-Sensitive Mutation, EGFR H773L, in a Chinese Patient With NSCLC

To the Editor:

EGFR mutations are key therapeutic driver mutations in NSCLC.1 The utilization of EGFR tyrosine kinase inhibitor (TKI) treatment largely relied on defined sensitive EGFR mutations (e.g., L858R); therefore, identifying novel, sensitive mutations has great therapeutic importance. Here, we present a patient with stage IV NSCLC with novel EGFR H773L mutation who obtained remarkable benefit from osimertinib treatment.

A 62-year-old woman was admitted to our hospital with complaints of irregular coughing and blood in sputum in June 2018. Computed tomography and whole-body bone scans revealed a lesion in the right lung and bone metastasis (Fig. 1A and B). Transbronchoscopic needle aspiration biopsy of lymph nodes yielded a diagnosis of NSCLC (Fig. 1C). Stage IV (T1bN2M1) NSCLC was thus diagnosed in the patient.

Next-generation sequencing was conducted, but only one unknown mutation—EGFR H773L—was identified. The patient thus received standard chemotherapy with pemetrexed plus cisplatin from July 2018. Unfortunately, the disease progressed quickly after two cycles of chemotherapy. A new lesion in the right lung and bilateral pleural and pericardial effusions were observed. The patient, considering her chemotherapy-insensitive status, received osimertinib (80 mg once a day) from August 19, 2018, on providing full consent. Soon, partial response was obtained within 1 month (Fig. 1D). The patient continued osimertinib treatment until 10 months later, when the right lower lung lesion progressed and the bilateral pleural and pericardial effusions in addition to the enlarged lymph nodes in the mediastinum and right hilum reappeared. Disease progression was thus considered.

In this case, the patient who failed chemotherapy obtained a considerable benefit from osimertinib with the progression-free survival exceeding 10 months. Conversely, the median overall survival of patients with stage IV NSCLC with bone metastasis is only 5 months and is even worse after chemotherapy failure.2 To our knowledge, this is the first report of a patient with NSCLC with EGFR H773L mutation who responded well to osimertinib.